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Laparoscopic adrenalectomy for co-secreting aldosterone and cortisol adenomas

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ABSTRACT

There are few published data on aldosterone and cortisol co-secreting adrenal tumours. Failure to perform comprehensive preoperative endocrine investigations in patients with adrenal "incidentalomas" or in those thought to be secreting only one hormone may account for this. Clinically patients with such lesions may have evidence of hypertension and hypokalaemia with no features of cortisol excess. Preoperative diagnosis of such lesions with accurate endocrinological work up is essential to prevent adrenal insufficiency and haemodynamic crises following removal of such glands.

We present a series of 4 patients with co-secreting tumours treated by laparoscopic adrenalectomy between September 2010 and March 2011. Our experience suggests that dual secretors are more common than originally thought. A high index of suspicion and adequate endocrine work up is paramount in diagnosing such tumours and in experienced hands, laparoscopic adrenalectomy with appropriate substitutive steroid cover is safe, feasible and curative for these functioning adrenal tumours.

1. Introduction

Adrenal adenomas are often discovered incidentally on abdominal imaging that has been performed for reasons other than suspected adrenal disease. Their incidence has been increasing proportionally to the use and sensitivity of radiographic imaging and is in the order of 4–6% of the imaged population.[1-3] These adenomas may be nonfunctional or hormonally active and malignant or benign. In clinical practice, it is essential to characterize the nature of these adenomas in order to treat them appropriately.

The optimal diagnostic approach to a patient with an adrenal incidentaloma is well established [Fig. 1][4] but not followed robustly. It is reasonable to start with a careful history and physical examination, focussing on the signs and symptoms suggestive of adrenal hyperfunction or malignant disease followed by imaging and hormonal testing.

The optimal treatment approach for these lesions is still being discussed. The general consensus is that small adrenal lesions with features typical of an adenoma and without biochemical abnormality can be safely left in-situ. Adrenal lesions with manifestations of hormonal excess need resection as do large [>4 cm] nonfunctioning adrenal lesions as they are considered potentially malignant.[5] The treatment for malignant lesions depends on the cell type, spread, and location of the primary tumour.[6] Other considerations include age, overall medical condition and patient anxiety.

In 1977, Hogan et al[7] reported a patient with an adrenal adenoma with concurrent production of cortisol and aldosterone. Since then, there have been a few case reports but there has been little published with regards to the surgical management of such lesions. This paper reports a series of 4 cases of aldosterone and cortisol co-secreting adrenal adenomas treated with a laparoscopic adrenalectomy between September 2010 and March 2011.

2. Case 1

A 73 year old man presented to the accident and emergency with a history of abdominal pain in January 2009. A computed tomography (CT) scan of the abdomen revealed a 1.9 cm well circumscribed lesion at the medial aspect of the right adrenal gland. It had Hounsfield units of −10 to −5 thus consistent with a right sided adrenal adenoma. On examination he did not have any features of Cushing's syndrome and his serum electrolytes were normal.

His past medical history included type 2 diabetes, hypertension, a coronary artery bypass graft following a myocardial infarction in 2009 and chronic kidney disease stage 3. Medications at the time of first endocrine review were atenolol, doxazosin, frusemide, spironolactone, lisinopril, nifedipine, insulin, metformin and asprin. It was arranged for him to have 24 h urine collection for catecholamines, overnight low dose dexamethasone suppression test (LDDST) and an aldosterone:renin ratio. His medications were stopped for the tests.

24 h urinary catecholamines were normal. The plasma aldosterone:renin ratio was high at 1300 suggesting hyperaldosteronism

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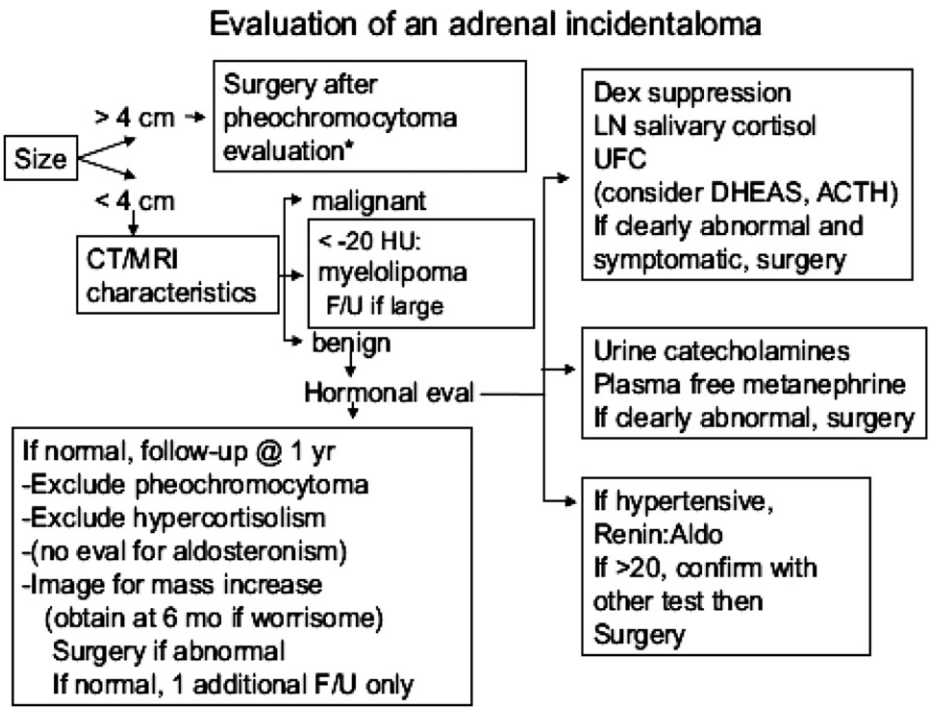

Fig. 1. Algorithm for the evaluation of an adrenal incidentaloma (4).

and serum cortisol after LDDST was 65 nmol/L suggesting that he had inadequate cortisol suppression. This indicated that he had concurrent secretion of aldosterone and cortisol from his adrenal adenoma.

A laparoscopic right adrenalectomy was performed in March 2011 with steroid cover. Histology confirmed a completely excised benign adrenocortical adenoma. Post operative recovery was uneventful and the patient was discharged home at day 4.

3. Case 2

A 85 year old woman was referred to us following an incidental finding of a right adrenal adenoma on CT performed for investigation of weight loss and a possible abnormality on the chest Xray. The left adrenal was normal. Past medical history included type 2 diabetes, hypertension and COPD. Medications included Doxazosin, Fosinopril, Frusemide, Glicazide, Aspirin and Seretide, Salbutamol and Spiriva inhalers.

Subsequent hormonal evaluation revealed an elevated plasma renin:aldosterone ratio suggestive of hyperaldosteronism. Despite the absence of full-blown clinical Cushing's syndrome, further investigations revealed suppressed basal ACTH levels, loss of diurnal rhythm of cortisol, and failure to suppress cortisol on LDDST, suggesting autonomous cortisol secretion by the tumour.

She underwent a right laparoscopic adrenalectomy in October 2010, with steroid cover. Histology confirmed a 8.3 cm completely excised benign adrenocortical adenoma. Post operative recovery was uneventful and the patient was discharged home at day 5. Complete clinical and biochemical remission of the disease was observed postoperatively.

4. Case 3

A 77 year old female was referred from a district general hospital for evaluation of a 12 cm adrenal mass discovered when a CT scan was obtained to evaluate abdominal pain and rectal bleeding. As well as being a lifelong smoker, she also had a 10 year history of hypertension and type 2 diabetes treated medically.

Endocrine evaluation revealed normal 24 h urinary catecholamines, raised plasma renin:aldosterone ratio and failure to suppress cortisol after a LDDST. These findings suggested that both cortisol and aldosterone were autonomously secreted from the tumour.

She underwent a right laparoscopic adrenalectomy in September 2010 with steroid cover. Despite the size of the lesion, conversion to open surgery was not required. Histology confirmed a 12 cm completely excised benign adrenocortical adenoma. She was monitored routinely in the Intensive Care Unit and subsequently discharged to the ward. Post operative recovery was complicated by a right lower lobe pneumonia which responded well to intravenous antibiotics and chest physiotherapy. She was discharged home 9 days after surgery.

5. Case 4

A 70 year old woman was referred by the urologists following an incidental finding of a mass adjacent to the upper pole of the right kidney in keeping with an adrenal adenoma on an ultrasound performed for investigation of suprapubic pain. Past medical history included hypertension, hypercholesteraemia and bilateral oophorectomy for ovarian cysts aged 48.

A subsequent CT revealed a 3.8 cm well circumscribed right adrenal mass. This was of low density, with the unenhanced attenuation values ranging from −8 to 2. In the portal phase it has an attenuation of up to 59. Based on its attenuation and features, this was in keeping with a benign adenoma. Further hormonal evaluation showed normal urinary metanephrines, failure to suppress cortisol adequately after a LDDST and a high plasma renin:aldosterone ratio.

She underwent an uneventful right laparoscopic adrenalectomy in October 2010, with steroid cover. Histology confirmed a 3.3 cm completely excised benign adrenocortical adenoma. Post operative recovery was uneventful and the patient was discharged home at 5 days.

6. Discussion

6.1. Imaging

The strength of any imaging test used to differentiate adrenal lesions will depend on its sensitivity and specificity. CT without intravenous contrast enhancement is usually sufficient as the initial study. If the adrenal mass is less than 10 Hounsfield units [HU], a diagnosis of adrenal adenoma can be made [71% sensitive, 98% specific].[8,9] All 4 of our patients had adrenal masses that were homogenous and hypodense with an unenhanced CT attenuation of less than 10 HU consistent with the diagnosis of adrenal adenomas Fig. 2.

If the adrenal mass is more than 10 HU, CT with intravenously administered contrast should follow, and the washout calculated; benign lesions typically demonstrate rapid washout of more than 50% [100% sensitive, 100% specific]. In cases in which CT findings are equivocal, chemical shift MRI can be performed. This reflects the lipid content of tissues, with lipid-rich adenomas losing signal intensity on out-of phase images.[8,9]

6.2. Hormonal testing

Although imaging phenotype is useful in predicting underlying pathology, it does not predict endocrine function. Functioning incidental adrenal adenomas are usually clinically silent, therefore biochemical investigation is warranted and evidence of hormonal excess must be sought. The most common disease states caused by functioning adenomas are Cushing's syndrome due to excess cortisol production and Conn's syndrome due to excess aldosterone production. Other secreted hormones include oestrogens, androgens, and 17-hydroxyprogesterone. These often manifest clinically and therefore do not require presumptive screening.

Approximately 5% of adrenal incidentalomas have been proved to be phaeochromocytomas and this needs to be excluded in all patients. The diagnosis is based on increased urinary catecholamine excretion and the optimal diagnostic protocol is to measure both free catecholamines and their metabolites the metanephrines.[10]

Clinically Silent Cushing's Syndrome refers to patients with autonomous cortisol secretion who do not have typical signs and symptoms of hypercortisolism. Although the obvious stigmata of Cushing's syndrome are absent, these patients may have the adverse effects of continuous, endogenous cortisol secretion, including hypertension, diabetes mellitus, obesity and osteoporosis.[11–13]

There is no consensus on the best evaluation for hypercortisolism. The Endocrine Society Clinical Practice guidelines published in 2008 suggest that the LDDST should be the first line screening test rather than urinary free cortisol which can be within the normal range.[14]

The overnight test is a simple outpatient test. Various doses of dexamethasone have been used, but 1 mg of dexamethasone is usually given between 2300 and 2400 h, and cortisol is measured between 0800 and 0900 h the following morning. Higher doses [1.5–2 mg] do not significantly improve the accuracy of the test.[15]

Primary Aldosteronism refers to patients with an inappropriately high aldosterone production, relatively autonomous from the renin-angiotensin system, and non suppressible by sodium loading. This inappropriate production of aldosterone causes cardiovascular damage, suppression of plasma renin, hypertension, sodium retention and potassium excretion that if prolonged and severe can lead to hypokalaemia. These patients have a higher cardiovascular morbidity and mortality than age- and sex-matched patients with essential hypertension and the same degree of blood pressure elevation and therefore normalization of circulating aldosterone levels or mineralocorticoid receptor blockade is warranted in these patients.[16,17]

The Endocrine Society Clinical Practice guidelines published in 2008 advocate screening for hyperaldosteronism in patients with an adrenal incidentaloma and hypertension, citing a prevalence of 1.1–10%.[18–23] Patients with an aldosterone producing adenoma may have normal levels of potassium in the blood, and therefore the measurement of potassium is not reliable in screening. The recommended test is the plasma aldosterone:renin ratio, using a sensitive renin assay and a diagnostic threshold of 20–40.[24]

6.3. Surgery

Laparoscopic adrenalectomy via the anterior transperitoneal approach was performed in all 4 cases. Operative times ranged from 70 to 125 min [average 100 min]. The harmonic scalpel was used for dissection and minimal blood loss encountered. There were no intraoperative complications.

None of the patients required conversion to an open procedure; in patient 3 where the tumour measured 12 cm, the gland was delivered by extending the optical incision to facilitate delivery without fracture of the lesion and in patient 1 extensive adhesions from previous surgery were dealt with laparoscopically. Length of stay ranged from 4 to 9 days. The only post operative complication

CT without intravenous contrast- 3.8cm adrenal mass <10 Hounsfield Units diagnostic of an adrenal adenoma (71% sensitive, 98% specific).

CT with intravenous contrast- Rapid washout of >50% diagnostic of a benign adenoma (100% specific, 100% sensitive).

Fig. 2. Pre and post contrast CT images for patient 4. CT without intravenous contrast-3.8 cm adrenal mass <10 Hounsfield units diagnostic of an adrenal adenoma (71% sensitive, 98% specific). CT with intravenous contrast-rapid washout of >50% diagnostic of a benign adenoma (100% specific, 100% sensitive).

noted in our case series was in patient 2 with a 40 pack year smoking history who developed a pneumonia that was treated conservatively.

Laparoscopic adrenalectomy was first performed and described in the literature by Gagner in 1992. Since then, this technique has become more and more widespread and there is general agreement that laparoscopic surgery is superior to open surgery and is now the 'standard of care'. It is associated with reduced analgesic requirements, improved patient satisfaction, a shorter hospital stay, and more rapid return to normal activities. It also yields the best cosmetic and long term results. A meta-analysis of 2625 laparoscopic adrenalectomies showed a mortality of 0.2% 1 month after surgery. Causes of death included haemorrhage, necrotizing pancreatitis, pulmonary embolism, sepsis and cardiopulmonary failure. The overall morbidity rate averaged 10%, with a higher rate in phaeochromocytoma and Cushing's syndrome.[25] In the long term, recurrence rates are not increased after laparoscopic removal.[26]

Although the current literature supports the fact that laparoscopy has replaced open surgery in the management of small and medium sized adrenal lesions, limited experience exists with large tumours [>10 cm]. It appears technical ability of the operator is the overriding factor as opposed to tumour size in making this decision.

6.4. Peri and post operative care

Patients are at risk of an Addisonian crisis once the functioning cortisol producing tumour is removed. This adrenal insufficiency is caused by corticotropin suppression and adrenal cortical atrophy of the contralateral adrenal gland.[27,28] There are no widely accepted guidelines for steroid substitutive therapy, and in our unit all patients receive 100 mg Hydrocortisone in theatre and post operatively, intravenous steroids are continued until the patients can eat and drink. As the contralateral gland may take up to a year to recover, oral longer term replacement with slow tapering is then commenced, for example fludrocortisone 50 mcg daily and oral hydrocortisone 10, 5 and 5 mg daily.

Thromboprophylaxis is also given in the peri and post operative period as these patients have an increased risk of thromboembolic complications. This because of a hypercoagulable state resulting from an increase in clotting factors such as factor VIII and von Willebrand factor, and by impaired fibrinolysis.[29]

Once discharged, patients are kept under close review by the endocrine unit. The short synacthen test is used to establish adrenal recovery and all patients in our series achieved endocrinological cure.

Surgery almost universally cures the hypokalemia if present but does not always cure the hypertension even in the setting of normalization of hormone levels postoperatively. The reason some patients have persistent hypertension is believed to be long-standing hypertension, presence of coexisting hypertension, age and a family history of hypertension.[10,26,30]

7. Conclusion

In conclusion, we believe that dual secreting adrenal adenomas may be underdiagnosed due to lack of appropriate endocrine work up before surgery. The numbers may be much higher than previously thought. We recommend that adrenal incidentalomas of any size should undergo hormonal testing according to the established protocols. Phaechromocytomas, hypercortisolism and hyperaldosteronism should be examined for in all cases.

Laparoscopic adrenalectomy is the treatment of choice for these dual secretor adenomas and it is vital that following removal of the functioning gland, the suppressed contralateral adrenal is covered with steroid substitutive therapy until function has recovered in order to prevent an Addisonian crisis.

Ethical approval

Not applicable.

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Author contribution

Lobo C—study design, data collection, data analysis and writing. Kolinioti A, Hainsworth A, Bano G, Mudan S, Sharma A—contributors.

Conflict of interest

None declared.

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